



PATENT  
ATTORNEY DOCKET NO.: 036249-5001

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:	)	
	)	
Peter A. FRISCHAUF et al.	)	Confirmation No. 4079
	)	
Application No.: 10/695,646	)	Group Art Unit: 1743
	)	
Filed: October 29, 2003	)	Examiner: Unassigned

For: METHOD OF PERFORMING CALIBRATION AND  
QUALITY CONTROL OF A SENSOR AND APPARATUS  
FOR PERFORMING THE METHOD

Commissioner for Patents  
Arlington, VA 22202

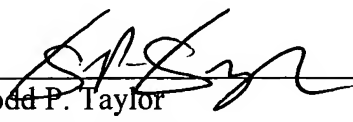
**CLAIM FOR PRIORITY**

Under the provisions of 35 U.S.C. §119, Applicants hereby claim the benefit of the filing date of **Danish** Patent Application No. PA 2002 01647 filed October 30, 2002 for the above-identified United States Patent Application.

In support of Applicants' claim for priority, filed herewith is a certified copy of the Danish application.

Respectfully submitted,

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Dated: March 9, 2004

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Patent application No.: PA 2002 01647

Date of filing: 30 October 2002

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Title: Metod of Performing Calibration and Quality Control of a Sensor and Apparatus Performing said Method

IPC: G 01 N 33/00; G 01 N 27/27; G 01 N 33/96; G 01 N 37/00

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.



**Patent- og Varemærkestyrelsen**  
Økonomi- og Erhvervsministeriet

06 November 2003

Pia Høybye-Olsen



**PATENT- OG VAREMÆRKESTYRELSEN**

## **Method of Performing Calibration and Quality Control of a Sensor and Apparatus Performing said Method**

The present invention relates to a method of performing calibration and quality control  
5 of a sensor for determining a parameter in a test fluid as well as an apparatus  
performing said method.

Sensors for measuring a parameter in a test fluid are widely used in various fields of  
industries. Examples of industries are the food industry, the environmental industry  
10 and the medical and the clinical industry, in particular the clinical laboratory industry.

In order to assure that sensor measurements are accurate it is required to regularly  
calibrate the sensors, i.e. to determine experimentally the correspondence between  
sensor responses and predetermined parameter values of the reference materials,  
15 usually by measurements on one or more reference materials.

In many cases it is also required to regularly control the quality of the sensor perform-  
ance, i.e. to verify experimentally that the sensor measurements are accurate and/or  
precise, usually by comparison of a measured parameter value of a reference material  
20 with an acceptance range of the same reference material.

In the food industry such routines of calibration and quality control are performed for  
instance on sensors for assessing milk quality. In the medical and clinical industry  
such calibration and quality control routines are performed for instance on sensors for  
25 determining parameters in physiological fluids.

DE 41 04 302 discloses a method of quality controlling and optionally calibrating a  
sensor for determining a parameter in a physiological fluid. According to the method  
one and the same volume of reference solution may be used to control and, if needed,  
30 to calibrate a measuring cell. The advantage of the invention is that the same  
reference solution may be used both in measuring cells for determining the hematocrit  
value and in cells for determining physiological electrolytes. In the method, however,  
the same volume of reference solution is used for both calibration and quality control  
of the sensor, and therefore the method does not provide for an independent  
35 assessment of sensor performance.

The general requirement to the reference materials for performing calibration and quality control routines is, that the reference material used in quality control of a sensor must be different from the reference material(s) used for the calibration upon  
5 which the quality control is based in order to ensure that the quality control procedure provides an independent assessment of sensor performance.

In the clinical and medical industry the legislation requires that sensors in addition to regular calibration procedures are exposed to quality control procedures. The quality  
10 control procedures must be performed often enough and covering a broad enough parameter range to be able to prove, at any time, that the sensor used is able to provide reliable data in its entire measuring range. This means that sensors must be checked by means of a system independent of the normal calibration system of the sensor.

15 It is accordingly recommended that in successive quality control cycles the quality of a sensor is controlled using a number of reference materials representing different parameter levels (often low, middle and high).

20 One and the same reference material may represent several different parameters at a time. This way calibration and/or quality control may be performed on several sensors simultaneously using only one reference material. The different levels of one parameter may be combined with any level of other parameters. An example of such a reference material is found in US 5,910,445 disclosing quality control liquids for use in  
25 the quality control procedure of electrochemical measuring apparatuses for measurement on physiological liquids.

Further, US 4,701,417 discloses calibration and control sera for use in lipid diagnosis. Solutions for calibrating and/or quality controlling sensors in blood gas analysers are  
30 disclosed in for example US 5,422,278 and US 5,910,445. In all cases the reference materials for calibration and the materials for quality control are described as two separate groups of reference materials.

In automatic apparatuses for blood gas analysis it is standard procedure to use at  
35 least five different reference materials in the calibration and quality control of the

respective sensors. En example is the blood gas analyser ABL™725 manufactured by Radiometer Medical A/S. In this apparatus several different blood parameters are determined. It contains two calibration solution containers which are integrated in the apparatus and which need to be renewed approximately once a month.

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In the ABL™725 the quality control may be performed manually at specific hours by aspirating reference solution from an ampoule by a specially trained operator. After shaking and breaking open the ampoule, it is provided with an adapter for attaching it to the inlet upon which an automated quality control procedure is initiated. When the  
10 operator has obtained a measuring result, he or she must control that the result fall within a certain acceptance range, which is given on an insert of the ampoule. It is recommended that reference materials of at least three different parameter levels are used.

15 Alternatively, the ABL™725 may be provided with a module (AutoCheck™) for automatic aspiration of control fluid from an ampoule for quality control of the apparatus. With this module the operator handling is reduced to removing a holder from the apparatus, loading the holder with ampoules and reinserting it. This must be done approximately once a week. The operator still needs to pay attention to the  
20 number of ampoules of each level he or she loads to the holder.

Thus, in the known methods of performing calibration and quality control of a sensor for determining a parameter in a test fluid, a substantive number of different reference materials are required. Also, the known methods require that a specially trained  
25 operator perform the quality control routine or at least once a week load a holder with ampoules for automatic aspiration of quality control fluid.

It is an object of the invention to provide a method of performing calibration and quality control of a sensor for determining a parameter in a test fluid in which method the  
30 number of reference materials may be reduced yet retaining the same precision and accuracy in the calibration and quality control and yet fulfilling the requirement that the reference material used in the quality control is different from the reference material(s) used in the calibration upon which the quality control is based.

It is a further object of the invention to provide an apparatus for determining a parameter in a test fluid which apparatus employs the method according to the invention for performing calibration and quality control of a sensor contained in said apparatus.

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It is yet another object of the invention to provide a method and an apparatus which allow automated handling of the quality control procedure of a sensor. Thus the requirement to maintenance and specially trained operators for operating such apparatuses is minimised as well as the risk of human errors.

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The object is achieved by providing a method of performing calibration and quality control of a sensor for determining a parameter in a test fluid which method is characterized in that a calibration and quality control cycle is repeated, a cycle comprising the steps of

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performing a calibration of the sensor using reference materials representing a parameter level, and

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performing a quality control of the sensor as calibrated using a reference material representing another parameter level than in the calibration step,

in which method

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in one cycle a reference material is used in the quality control step which in a previous cycle was used in the calibration step.

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The method according to the invention has the advantage that the number of reference materials can be reduced by using the same reference materials both for calibration and for quality control purposes without reducing the quality of the calibration and the quality control and yet retaining the independency between the calibration system and the quality control system. The only requirement is that one and the same reference material is not used both in the quality control step and in the calibration step upon which the quality control is based.

A reduction in the number of reference materials makes it possible to reduce the storage space for reference material. If this space is inside an apparatus provided with the sensor, the size of the apparatus may be reduced.

- 5 The fully automated handling of the quality control procedure of a sensor has the advantage that the requirement of specially trained operators for operating such apparatuses is minimised as well as the risk of human errors.

The test fluid to be analysed may be any fluid in which it is desired to determine a  
 10 parameter. Examples are fluids in food processing, such as beer, milk and meat processing fluids, and physiological fluids, such as whole blood, blood plasma, serum, cerebrospinal fluids, spit and urine.

The parameter towards which the sensor may be specific may be any parameter of  
 15 interest, for example:

viscosity, density, pressure, conductivity, and surface tension.

Of particular interest are parameters of physiological fluids such as

20 pH, concentrations of electrolytes, such as  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$  and  $\text{NH}_3$  ( $\text{NH}_4^+$ ), concentrations of dissolved gases, notably oxygen and carbon dioxide (conventionally reported in the form of partial pressures, e.g.  $p\text{O}_2$ ,  $p\text{CO}_2$ ), hematocrit (Hct), concentration of haemoglobin and haemoglobin derivatives,  
 25 such as oxyhaemoglobin, deoxyhaemoglobin, methaemoglobin, carboxyhaemoglobin, sulfhaemoglobin and fetal haemoglobin, concentrations of metabolic factors, such as glucose, creatinine, urea (BUN), uric acid, lactic acid, pyruvic acid, ascorbic acid, phosphate, protein, bilirubin, cholesterol, triglycerides, phenylalanine and tyrosine, concentrations of enzymes, such as  
 30 lactic acid dehydrogenase (LDH), lipase, amylase, choline esterase, alkaline phosphatase, acid phosphatase, alanine amino transferase (ALAT), aspartate amino transferase (ASAT) and creatinine kinase (CK), and concentrations of ligands, such as antibodies and nucleotide fragments.

- 35 As used here, the term "sensor" denotes any kind of organ of which some part, in the present context called the sensing part, is capable

either of

- 5 selectively interacting with the chemical species of interest, thereby producing a well-defined and measurable response which is a function of the desired characteristic of that chemical species, the desired characteristic thus being derivable therefrom,

or of

- 10 responding to a bulk property of a fluid, the response not being selective with respect to any specific chemical species, but being a function of the total concentration of one or more chemical species in the liquid, the desired characteristic thus being derivable therefrom.

- 15 Relevant types of sensors are those adapted to determine any of the previously mentioned parameters, for example:

20 potentiometric sensors for use in aqueous media, such as ion-selective electrodes for specific measurement of the concentration of selected ionic chemical species, the response being in the form of an electric potential, amperometric sensors, such as sensors for the determination of oxygen partial pressure, whose response is in the form of an electric current, optical sensors, such as sensors producing a colour response to a particular chemical species, the response being measured spectrometrically using reflectance or transmittance, 25 and the colour response being a colour intensity or the decay of colour intensity, piezoelectric sensors, thermometric sensors, pressure-change sensors, acoustic sensors, enzyme-based sensors employing an enzymatic reaction and generating a response on the basis of any relevant physical principle, for example any of those principles employed in the sensor types listed above; 30 examples are enzyme-based thermistors and enzyme-based amperometric sensors for use in the measurement of concentrations of metabolic products, e.g. glucose, urea, creatinine or lactate, and affinity sensors comprising one moiety of an affinity pair, e.g. an antigen/antibody pair or two complementary nucleotide fragments, the other moiety being the chemical species of interest.

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The sensor may be of any design. Preferably it is a miniaturized, planar sensor, but also conventional sensors are suitably calibrated and quality controlled by the method according to the invention.

- 5 Sensors generally perform a conversion function to convert the energy form associated with the change occurring at the surface of the sensing part to electrical energy or electromagnetic radiant energy, the sensor response thereby being registerable in the form of an electrical or optical signal.

- 10 The measured sensor response may be a one-point measurement or a transient.

A "calibration" of the sensor is to be understood as an experimental determination of the correspondence between the sensor responses and predetermined parameter values of a reference material. Usually, said correspondence is found by obtaining

- 15 sensor responses to one or more reference materials having predetermined parameter values and determining the correspondence between those.

Said correspondence is most often expressed as a regression function calculated from the predetermined parameter values and the corresponding sensor responses.

- 20 Alternatively, if the measuring results are shown directly on a graduated scale, the graduated scale may be moved to show the predetermined parameter value of the reference material.

The correspondence determined in the above calibration is then used when a

- 25 parameter in a test fluid is to be determined. First a sensor response to the test fluid is obtained. Then the sensor response is converted into a measured parameter value by using the correspondence determined.

The conversion may be effected by programmed control means comprising an algorithm to provide a measured parameter value. The algorithm is adjusted in each calibration step.

- 35 In the method of the invention any number of reference materials may be used in the calibration step. The number of reference materials which are required to obtain a reliable calibration of a sensor depend on the nature of the sensor and of the demands to accuracy and/or precision. It is thus preferred to use reference materials

representing one to five different parameter levels, more preferred one to three different levels in the calibration step.

5 It may be sufficient to initially calibrate the sensor once using more than one reference material. Any subsequent calibrations may then be performed using only one reference material and is simply used to correct the previously determined correspondence between sensor responses and predetermined parameter values.

10 However many sensors need to be calibrated regularly using reference materials representing at least two parameter levels. A calibration using reference materials representing more than two parameter levels may in some cases provide a more reliable calibration.

15 One of the reference materials used in the calibration of the sensor may be a blank. That is, it may represent a parameter level of "zero".

20 A "quality control" of the sensor is to be understood as the experimental verification that the sensor measurements are accurate and/or precise. Usually said verification is performed by controlling whether a measured parameter value of a reference material is within an acceptance range thereof. The measured parameter value of the reference material is obtained by converting the sensor response into the measured parameter value using an algorithm as described above. It is then controlled whether the measured parameter value is within the acceptance range.

25 The acceptance range is centered around a predetermined parameter value. The limits of the range depend i.a. on sensor variation, on the variation when determining the predetermined parameter value of the reference materials for both the quality control and the calibration and/or demands to accuracy and precision.

30 A "calibration and quality control cycle" is to be understood as one calibration and one quality control where the correspondence determined in the calibration is used in said cycle for converting the sensor response to the reference material of the quality control into a measured parameter value.

If a total of more than two reference materials are used in the method all may be used in each calibration and quality control cycle, or a selection among the total number of reference materials may be used in each cycle. The only demand is that the total number of reference materials at least equals the number of quality control levels  
5 desired.

There is no demand as to any time interval between the calibration and the quality control, nor to the time interval between two cycles. If it is desired to control performance of the sensor and the apparatus as well as the quality of the reference  
10 materials, the quality control should preferably be performed fairly shortly after the calibration upon which the quality control is based. If it is desired to control the drift of a sensor within a certain period of time the calibration upon which the quality control is based should preferably be performed at the beginning of said period and the quality control at the end of said period.

15 Between one cycle of calibration and quality control and a previous cycle of calibration and quality control supplementary calibrations and/or quality controls may be performed on the same or different reference materials.

20 In this context the "previous cycle" denotes a cycle, which is carried out any number of cycles before the cycle in question.

The order in which the individual steps of the method are performed is not important. The only demand is that the correspondence of the calibration upon which the quality  
25 control is based must be obtained before the measured parameter value may be obtained in the quality control.

A "reference material" is a material representing an exact parameter value. It is preferred that the reference material retains a constant value for an extended period of  
30 time. The reference material may include the test species itself or a means simulating the test species. Reference materials for use in the same cycle must be prepared independently of each other in order to provide an independent assessment of sensor performance.

Such reference material preferably has a "predetermined parameter value". This may be the experimental determination of the parameter value itself, or it may be the same adjusted to take into account various systematic errors in the measuring method.

5 Examples of such errors affecting systematically the measured result are the nature of the test fluid and the apparatus and the sensor with which the test fluid is analysed as well as residues near the sensor surface and measurements performed before equilibrium is obtained at the sensor surface.

10 Since the procedure of performing the calibration may deviate from that of the quality control, the predetermined parameter value for use in the quality control may deviate from the one for use in the calibration of the same reference material, the two values taking into account different systematic errors.

A reference material may be referred to as representing or having a parameter "level".  
15 This level is to be understood as an approximate parameter value of a given reference material, the exact parameter value lying in the neighbourhood of said level.

In a full calibration and quality control routine, the cycle is repeated until all available reference materials have been used once for the quality control of the sensor  
20 performance. Thus the performance of the sensor is controlled at all the different parameter levels in one routine providing a more reliable quality control of the sensor.

Preferably this routine is systematically repeated, making the method even more suitable for being automatically performed.

25 The correspondence determined in the above calibration step may be a first calibration for performing the quality control of the sensor. Subsequently, a second calibration may be performed in the same cycle based on the same reference materials as were used in the first calibration and the quality control. The correspondence of the second  
30 calibration may then be used when a parameter in a test fluid is to be determined.

By doing this a second calibration is obtained which includes one more calibration point than the first one without increasing the total number of reference materials. Such calibration provides in some cases measured parameter values with less  
35 variation than the first calibration does.

Said second calibration may be performed in various ways. In one embodiment, a cycle comprises obtaining sensor responses to the reference materials used in the first calibration step and the quality control step, obtaining a further sensor response to the reference material used in the quality control step, and performing a second calibration based on the sensor responses obtained in the first calibration step and on the further sensor response obtained. This embodiment is preferred if the procedure of performing the quality control measurement is different from the procedure of performing the calibration measurement.

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According to another embodiment the second calibration is based on the sensor responses obtained in the first calibration step and in the quality control step. Thus the step of performing the second calibration only includes performing a second calculation of the correspondence between sensor responses and predetermined parameter values not a second round of measurements.

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The introduction of a step of performing a second calibration into a calibration and quality control of a sensor even without the previously described cyclic use of the reference materials may result in a reduction in the use of reference materials, if the same reference materials are used in the second calibration as were used in the first calibration.

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Accordingly the object may further be achieved by providing a method of performing calibration and quality control of a sensor for determining a parameter in a test fluid comprising the steps of

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performing a first calibration of the sensor using a reference material representing a parameter level,

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performing a quality control of the sensor as calibrated using a reference material representing another parameter level than in the calibration step, and

performing a second calibration of the sensor using the same reference materials as were used in the steps of performing the first calibration and the quality control.

- 5 The method according to the invention has the advantage that the number of reference materials can be reduced by using the same reference materials in a second calibration as were used in the first calibration and quality control purposes without reducing the quality of the calibration and the quality control and yet retaining the independency between the calibration system and the quality control system. Actually  
10 an improved calibration is obtained without using any supplementary reference materials.

- For some optical sensors the reference materials may be a solid brick or filter containing a colour inducing material. In apparatuses designed for analysing fluids,  
15 however, it is preferable that the reference materials are fluids.

- If the reference material is a fluid, the fluid may also contain constituents having a rinsing action. Thus a separate rinsing or cleaning solution may be omitted or used more rarely.  
20

- A reference material may represent more than one parameter. This is an advantage if it is desired to determine several different parameters in one sample of test fluid and thus to calibrate or quality control more than one sensors simultaneously. If the reference material represents different parameters at various relevant levels it is  
25 possible to calibrate or quality control all sensors at one level in one operation. Many automatic analysers perform simultaneous multi analyte determination of a test fluid. One example is a blood gas analyser, such as the above-mentioned ABL™725.

- The total range of the parameter levels of the reference materials should in the present  
30 method essentially cover the specified measuring range of the sensor. This is in order to ascertain that the measurements are reliable in that range.

- Also, the distribution of the respective parameter levels of the various reference materials within said total range may influence the reliability of the quality control. If the  
35 correspondence determined in the calibration is used for conversion of a sensor

response into a measured parameter value, which lies outside the calibration range, the uncertainty of the determination will be greater the farther away from the calibration the measured or predetermined parameter value is.

- 5 If in a cycle the parameter levels of the reference materials used for performing the calibration upon which the quality control is based define a calibration range, and the parameter levels of all the reference materials used in said cycle define a total range, it is preferred that said calibration range is at least one fourth of said total range. It is particularly preferred that said calibration range is at least one third of said total range.

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The method according to the invention is particularly suitable for performing calibration and quality control of a sensor for determining a blood parameter, since it fulfils the legal requirements to calibration and quality control in the clinical field, is reliable and requires only limited maintenance from the operator and not at specific hours of the day. It will often be sufficient to renew the containers of reference fluid once or twice a month.

15

Further the containers may be provided in a cartridge and thus can be renewed without the operator having any prior knowledge as to the choice of containers or to the correct connection of the containers to the apparatus.

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Thus, according to a preferred embodiment of the invention the parameter to be determined is a blood parameter, such as pH,  $p\text{CO}_2$  and  $p\text{O}_2$ , electrolytes such as  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$  and  $\text{NH}_4^+$ , haemoglobin, haemoglobin derivatives, Hct, or metabolic factors, such as bilirubin, glucose, lactate or creatinine.

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According to another aspect of the present invention, an apparatus is provided for determining a parameter in a test fluid comprising

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programmed control means for controlling the functioning of the apparatus,

a sensor for obtaining a response to the parameter in the test fluid,

means for exposing the sensor to a sample of the test fluid,

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reference materials representing at least two different parameter levels,

means for exposing the sensor to the reference materials,

5 means for processing a sensor response of the sensor into a measured parameter value,

means for reporting a measured parameter value,

10 the programmed control means controlling the method of performing a calibration and quality control of the sensor according to the method of the invention.

The apparatus according to the invention has the advantage that the number of refer-  
15 ence materials may be reduced yet retaining the same precision and accuracy in the calibration and quality control and yet fulfilling the requirement that the reference material used in the quality control based upon a calibration is different from the reference material(s) used in the same calibration.

20 A reduction in the number of reference materials makes it possible to reduce the storage space for reference material. Inside the apparatus the storage requirement may also be reduced thus reducing the size of the apparatus.

Further, the method according to the invention provides a fully automated quality con-  
25 trol routine, thus minimising the requirements to maintenance and specially trained operators for operating such apparatuses. Also, the risk of human errors is minimised.

The terms "parameter", "test fluid", "sensor", and "reference material" are to be under-  
stood as having the same meanings as explained above.

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The sensor "response" is to be understood as the energy formed in association with the change occurring at the sensing surface or as said energy converted into electrical energy or electromagnetic radiant energy which is registerable by conventional converters.

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The apparatus may comprise more than one sensor. Preferably each sensor is specific towards one of the above-mentioned parameters.

5 The sensors are preferably miniaturized planar sensors which may be located in a cassette for simultaneous renewal of the whole cassette.

The "means for exposing the sensor to the test fluid" may for instance comprise inlet means for introducing the test fluid into the apparatus. The inlet means may be designed to receive the outlet opening of a sample container such as a syringe or a  
10 capillary or a specially designed sample container.

The "means for exposing the sensor to the test fluid" may further comprise an inlet probe for aspirating the sample of test fluid into the apparatus. Alternatively, the inlet may lead directly to a measuring chamber. The inlet or the inlet probe may be in fluid  
15 tight communication with a conduit. The conduit may comprise measuring chambers. It is preferably a tubing or a channel providing a fluid-tight path for transport of fluid through the conduit. The fluid may be transported through the conduit by means of a pump.

20 The sensor is exposed to the test fluid, either directly in the conduit or in a measuring chamber. The exposure of the sensor to the test fluid may be a direct physical contact between the sensing surface and the test fluid or it may be an indirect contact, the wall of the conduit or the measuring chamber separating the sensing surface from the test fluid. If optical sensing methods are employed, this part of the wall should be  
25 transparent to the type of radiation used.

The reference materials may be solid or fluid and contain any of the parameters mentioned earlier. A total of two or three reference materials are preferred, but one or more further reference materials for calibrating the sensor may be included.

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The "means for exposing the sensor to the reference material" may be the same as the "means for exposing the sensor to the test fluid". It should however also include a mechanical device, which is capable of moving reference material from a storage location to a location providing operational communication between the sensor surface

and the reference material. If the reference materials are fluid the device is preferably a pump, if they are solid the device is preferably a robot arm.

5 The "means for processing a sensor response of the sensor into a measured parameter value" preferably comprises an operational amplifier for amplifying and converting the sensor response as well as an appropriate algorithm and software for executing the processing of the signal. The nature of the sensor response amplifier naturally depends on the nature of the sensor. The algorithm for converting the amplified sensor response into a measured parameter value may comprise the  
10 correspondence determined in the calibration and appropriate adjustments taking into account diverse systematic errors in the measuring method. Examples are given above.

15 The "means for reporting a measured parameter value" may for example be a scale, a display, a printer, or a digital voice reporting the measured parameter value obtained from the processing means.

20 The parts of such an apparatus being in contact with test fluid and/or reference fluid are often referred to as belonging to the "wet section" of the apparatus. This wet section may be an integral part of the apparatus or it may be provided in the form of a separate container such as a cassette. The cassette may comprise several measuring chambers and/or sensors.

25 Preferably all the reference materials are located in a cartridge. Thus instead of changing one bag or bottle of reference material at a time, all two or more reference materials may be renewed in one operation. This provides a more user-friendly renewal of reference materials. The cartridge may also contain a waste bag into which the used reference materials and the used samples of test fluid are discarded.

30 When a parameter level of a test fluid is to be determined a sample of the test fluid is introduced into an apparatus as described above and the analysis of the sample is being performed automatically. The reported measured parameter value is obtained from the apparatus.

35 The apparatus according to the invention preferably is a blood analyser.

The invention will now be explained in detail by means of examples of embodiments and with reference to the drawing in which

5 Fig. 1 is a schematic drawing of the modified wet section of an automatic blood gas analyser of the invention

Fig. 2 is a chart representing the first calibration curve and corresponding quality control as well as the second calibration curve for a pH sensor.

10 According to a preferred embodiment of the invention the method of performing calibration and quality control of a sensor is applied to a blood analyser having a wet section as shown in Fig. 1.

In Fig. 1 an inlet module 1 provides test fluid access to the apparatus. The inlet  
15 module 1 comprises an inlet gasket 2 provided with a cone for receiving the Luer of a syringe and a cone for receiving a capillary. A channel is leading from the cones through the gasket 2 to an inlet probe 3. If a syringe containing test fluid is connected to the inlet gasket 2, the inlet probe 3 may be displaced into the syringe and a sample of test fluid aspirated into the apparatus. The inlet gasket 2 is further provided with a  
20 tubing 4 and pump 5 for collecting any sample spills into a waste container 10.

The sample is transported through the tubing 6 to a measuring section 7 by means of pumps positioned after the measuring section, the pumps being represented by the pump 8. The measuring section 7 is thermostatically controlled at 37 °C. The  
25 measuring section 7 comprises sensors selective towards pH, CO<sub>2</sub>, O<sub>2</sub>, Cl, Ca, Na, K, glucose, lactate sensors, a reference sensor, and an oxymetry module.

After analysis the sample is transported through the tubing 9 by means of the pump 8 to the waste container 10.

30

The wet section further comprises a liquid cartridge 14 containing reference fluid containers 11, 12 or 13, tubing 15, a pump 16, and an air inlet 17.

When a calibration or quality control measurement is performed, a sample of reference  
35 fluid is transported from one of the respective reference fluid containers 11, 12 or 13,

contained in the liquid cartridge<sup>14</sup> through the tubing <sup>15</sup> to the measuring section <sup>7</sup> by means of the pumps <sup>16</sup> and <sup>8</sup>. After analysis the sample is transported to the waste container <sup>10</sup> as described above.

- 5 After each measurement a rinsing procedure is performed. The measuring section <sup>7</sup> is flushed with one of the reference fluids <sup>11</sup>, <sup>12</sup> or <sup>13</sup> further comprising components with rinsing action. The air inlet <sup>17</sup> is used for introducing air bubbles into the stream of calibration solution when a rinsing procedure is performed. This provides a better cleaning action.

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In the following non-limiting example, reference fluids are prepared as described in US 5,910,445. The compositions are as follows:

chemical species	Ref. 1	Ref. 2	Ref. 3	Unit
MOPS	51.9642	27.9425	37.5593	mmol/kg H <sub>2</sub> O
NaOH	32.8466	9.0839	30.1676	mmol/kg H <sub>2</sub> O
NaCl	104.5205	61.7754	142.1083	mmol/kg H <sub>2</sub> O
KCl	4.2818	7.5475	2.1564	mmol/kg H <sub>2</sub> O
CaCl <sub>2</sub>	0.9587	1.5985	0.3875	mmol/kg H <sub>2</sub> O
NaHCO <sub>3</sub>	11.7346	12.3584	9.4234	mmol/kg H <sub>2</sub> O
glucose	0.0	15.4784	7.2232	mmol/kg H <sub>2</sub> O
Na-lactate	0.0	9.6192	4.8096	mmol/kg H <sub>2</sub> O
Na-sulforhodamin	0.0	1.6705	2.5059	mmol/kg H <sub>2</sub> O

Table 1: Compositions of reference fluids.

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The above compositions provide reference fluids with predetermined parameter values for calibration purposes as given below in table 2:

Parameter	Ref. 1	Ref. 2	Ref. 3	Unit
pH	7.200	6.800	7.600	
pCO <sub>2</sub>	30.0	70.0	10.0	mmHg
pO <sub>2</sub>	170.0	90.0	50.0	mmHg
cK <sup>+</sup>	4.0	7.0	2.0	mmol/L
cNa <sup>+</sup>	140.0	90.0	180.0	mmol/L
cCa <sup>++</sup>	0.8	1.65	0.40	mmol/L
cCl <sup>-</sup>	100.0	65.0	130.0	mmol/L
cGlu	0	15	7	mmol/L
cLac	0	8	4	mmol/L
tHb	0	9	12	mmol/L

Table 2: Predetermined parameter values for calibration purposes of reference fluids.

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The acceptance ranges of these reference fluids for quality control purposes are as follows:

Parameter	Ref. 1	Ref. 2	Ref. 3	Unit
pH	7.163 - 7.203	6.785 - 6.825	7.560 - 7.600	
pCO <sub>2</sub>	26.4 - 32.4	61.8 - 71.8	8.8 - 12.8	mmHg
pO <sub>2</sub>	158 - 178	82 - 102	55 - 75	mmHg
cK <sup>+</sup>	3.3 - 3.9	6.0 - 6.6	1.7 - 2.3	mmol/L
cNa <sup>+</sup>	125 - 134	75 - 85	163 - 168	mmol/L
cCa <sup>++</sup>	0.69 - 0.89	1.48 - 1.68	0.33 - 0.53	mmol/L
cCl <sup>-</sup>	90 - 102	61.0 - 73.0	120 - 132	mmol/L
cGlu	0 - 1	13.1 - 15.1	5.4 - 7.4	mmol/L
cLac	0 - 1	6.4 - 7.4	2.7 - 3.7	mmol/L
tHb	0 - 0.6	8.4 - 9.6	11.3 - 12.7	mmol/L

Table 3: Acceptance ranges for quality control purposes of reference fluids.

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A first cycle of calibration and quality control is initialised by running an analysis of each of the three reference fluids Ref. 1, Ref. 2 and Ref 3.

The wet section including measuring chambers is flushed with reference fluid Ref. 1 in an amount corresponding to approximately twice the volume of the wet section. The wet section is filled again upon which sensor measurements are recorded every second for 30 seconds. This is a calibration measurement (Cal).

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The above is repeated with Ref. 2.

Then the wet section is filled with a sample of reference fluid Ref. 3 and sensor measurements are recorded every second for 30 seconds. The wet section is flushed with reference fluid Ref. 3 in an amount corresponding to approximately the volume of the wet section. The wet section is filled again with Ref. 3, and sensor measurements are recorded every second for another 30 seconds. The first of the measurements is a quality control measurement (QC) and the second measurement is a calibration measurement (Cal).

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After approximately eight hours the above cycle is repeated except that the double measurement is performed on Ref 2. After another eight hours the above cycle is repeated except that the double measurement is performed on Ref 1

20 In the following, the example is explained only with regard to the parameter pH. However the results of the measurements of any of the other parameters may be processed similarly. The obtained measured parameter values of pH are:

Parameter	Ref. 1	Ref. 2	Ref. 3	Ref. 1	Ref. 2	Ref. 3
	QC measurements			calibration measurements		
Cycle 1	-	-	7.575	7.195	6.804	7.602
Cycle 2	-	6.805	-	7.200	6.800	7.601
Cycle 3	7.189	-	-	7.205	6.798	7.605

Table 4: Measured parameter values of pH in cycle 1, 2 and 3.

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In cycle 1 a first calibration is obtained by estimating the correspondence between the predetermined parameter values (PPV) and the measured parameter values (MPV) of Ref. 1 and Ref. 2. The measured QC parameter level (MPV) of Ref. 3, which is obtained using the first calibration, is then compared to the assigned parameter level (PPV) with acceptance limits. This is depicted in Fig. 2.

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As shown in Fig. 2 the QC parameter level of pH is within the acceptance limits and the quality control is accepted.

- 5 Subsequently, a second calibration is obtained based on all three calibration measurements, which second calibration may be used in determining measured parameter values of a test fluid. This second calibration curve is also depicted in Fig. 2.
- 10 The results of the two other cycles may be processed similarly. All quality controls fall within the acceptance limits as can be deduced from table 4.

If three reference materials are used, the full routine of calibration and quality control comprises at least three cycles. The reference materials may be combined in a  
 15 number of ways. A few combinations are exemplified below. The cycles a, b and c may be performed in any order.

Cycle number	Ref. 1	Ref. 2	Ref. 3
A	QC	cal	cal
B	cal	cal	QC
C	cal	QC	cal

Table 5. In all cycles the quality control is based on a two-point calibration.

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Cycle number	Ref. 1	Ref. 2	Ref. 3
A	-	QC	cal
B	cal	-	QC
C	QC	cal	-

Table 6. Three reference materials are used, but in every cycle one reference material is "dummy".

Cycle number	Ref. 1	Ref. 2	Ref. 3
A	QC	QC	cal
B	cal	QC	QC
C	QC	cal	QC

Table 7. Quality control is performed in two points in every cycle, and calibration in one point.

Cycle number	Ref. 1	Ref. 2	Ref. 3
A	cal	QC	cal
B	cal	-	QC
C	cal	cal	-

- 5 Table 8. In some areas of the total range it is preferred that the quality control is based on a two-point calibration, in others a one point calibration is sufficient.

- If more than three reference materials are used in the method, a further calibration point may be introduced and/or a second quality control may be performed. Optionally,
- 10 some cycles of a full routine of calibration and quality control may include the further reference material(s) whereas they are left out in other cycles.

- If four reference materials are used, the full routine of calibration and quality control comprises at least four cycles. The reference materials may be combined in a number
- 15 of ways. A few combinations are exemplified below. The cycles a, b, c and d may be performed in any order.

Cycle number	Ref. 1	Ref. 2	Ref. 3	Ref. 4
A	cal	cal	cal	QC
B	cal	cal	QC	cal
C	cal	QC	cal	cal
D	QC	cal	cal	cal

Table 9. In all cycles a three-point calibration is performed.



Cycle number	Ref. 1	Ref. 2	Ref. 3	Ref. 4
A	-	QC	cal	cal
B	cal	-	QC	cal
C	cal	cal	-	QC
D	QC	cal	cal	-

Table 10. Four reference materials are used, but in every cycle one reference material is "dummy".

Cycle number	Ref. 1	Ref. 2	Ref. 3	Ref. 4
A	QC	QC	cal	cal
B	cal	QC	QC	cal
C	cal	cal	QC	QC
D	QC	cal	cal	QC

5 Table 11. Quality control is performed at two levels in every cycle.

Cycle number	Ref. 1	Ref. 2	Ref. 3	Ref. 4
A	cal	QC	cal	cal
B	cal	-	QC	cal
C	cal	cal	-	QC
D	QC	cal	cal	-

Table 12. In some areas of the total range it is preferred that a three-point calibration is performed, in others a two-point calibration is sufficient.

**CLAIMS**

1. A method of performing calibration and quality control of a sensor for determining a parameter in a test fluid in which method a calibration and quality control cycle is repeated, a cycle comprising the steps of
  - performing a calibration of the sensor using a reference material representing a parameter level, and
  - performing a quality control of the sensor as calibrated using a reference material representing another parameter level than in the calibration step,in which method
  - in one cycle a reference material is used in the quality control step which in a previous cycle was used in the calibration step.
2. The method according to claim 1 characterized in that reference materials representing two different parameter levels are used in the calibration step.
3. The method according to claim 2 characterized in that additional reference materials representing one or more further parameter levels are used in the calibration step.
4. The method according to any of the preceding claims characterized in that the cycle is repeated until each of the reference materials have been used once for quality control of the sensor.
5. The method according to any of the preceding claims characterized in that in a cycle the calibration performed in the calibration step is a first calibration and that the cycle further comprises the step of
  - performing a second calibration of the sensor using the same reference materials as were used in the first calibration step and in the quality control step.

6. The method according to claim 5 characterized in that in a cycle

5                    sensor responses are obtained to the reference materials used in the first calibration step and the quality control step,

                  a further sensor response is obtained to the reference material used in the quality control step, and

10                the second calibration is based on the sensor responses obtained in the first calibration step and on the further sensor response obtained.

7. The method according to claim 5 characterized in that in a cycle

15                    sensor responses are obtained to the reference materials used in the first calibration step and the quality control step, and

                  the second calibration is based on the sensor responses obtained in the first calibration step and the quality control step.

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8. The method according to any of the preceding claims characterized in that in a cycle

25                    the parameter levels of the reference material used for performing the calibration upon which the quality control is based define a calibration range,

                  the parameter levels of all the reference materials used in said cycle define a total range, and

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                  said calibration range is at least one fourth of said total range.

9. The method according to claim 8 characterized in that said calibration range is at least one third of said total range.

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10. A method of performing calibration and quality control of a sensor for determining a parameter in a test fluid comprising the steps of

5 performing a first calibration of the sensor using a reference material representing a parameter level,

performing a quality control of the sensor as calibrated using a reference material representing another parameter level than in the calibration step, and

10 performing a second calibration of the sensor using the same reference materials as were used in the steps of performing the first calibration and the quality control.

15 11. The method according to claim 10 characterized in that

sensor responses are obtained to the reference material used in the first calibration step and the quality control step,

20 a further sensor response is obtained to the reference material used in the quality control step, and

the second calibration is based on the sensor responses obtained in the first calibration step and on the further sensor response obtained.

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12. The method according to claim 10 characterized in that

sensor responses are obtained to the reference material used in the first calibration step and the quality control step, and

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the second calibration is based on the sensor responses obtained in the first calibration step and the quality control step.

13. The method according to any of claims 10 - 12 characterized in that

5           the parameter levels of the reference materials used for performing the calibration upon which the quality control is based define a calibration range,

          the parameter levels of all the reference materials used define a total range, and

10           said calibration range is at least one fourth of said total range.

14. The method according to any of the preceding claims characterized in that the parameter is a blood parameter.

15           15. An apparatus for determining a parameter in a test fluid comprising

          programmed control means for controlling the functioning of the apparatus,

          a sensor for obtaining a response to the parameter in the test fluid,

20           means for exposing the sensor to a sample of the test fluid,

          reference materials representing at least two different parameter levels,

25           means for exposing the sensor to the reference materials,

          means for processing a sensor response of the sensor into a measured parameter value, and

30           means for reporting a measured parameter value,

wherein

the programmed control means control the execution of a method of performing a calibration and quality control of the sensor according to any of the preceding claims.

- 5        16. The apparatus according to claim 15 characterized in that the apparatus comprises reference materials representing at least three different parameter levels.
- 10       17. The apparatus according to claims 15 or 16 characterized in that at least two reference materials are located in one and the same cartridge.
18. The apparatus according to any of claims 15 - 17 characterized in that the sensor is a miniaturized planar sensor.
- 15       19. The apparatus according to any of claims 15 - 18 characterized in that the sensor is located in a cassette.
20. The apparatus according to any of claims 15 - 19 characterized in that the apparatus is a blood analyzer.
- 20

TITLE

**5 ABSTRACT**

The present invention provides a method of performing calibration and quality control of a sensor for determining a parameter in a test fluid in which method a calibration and quality control cycle is repeated. A cycle comprises the steps of performing a calibration and a quality control of the sensor using independent reference materials. In the method a reference material is in one cycle used in the quality control step which in a previous cycle was used in the calibration step. The present invention further provides an apparatus performing said method

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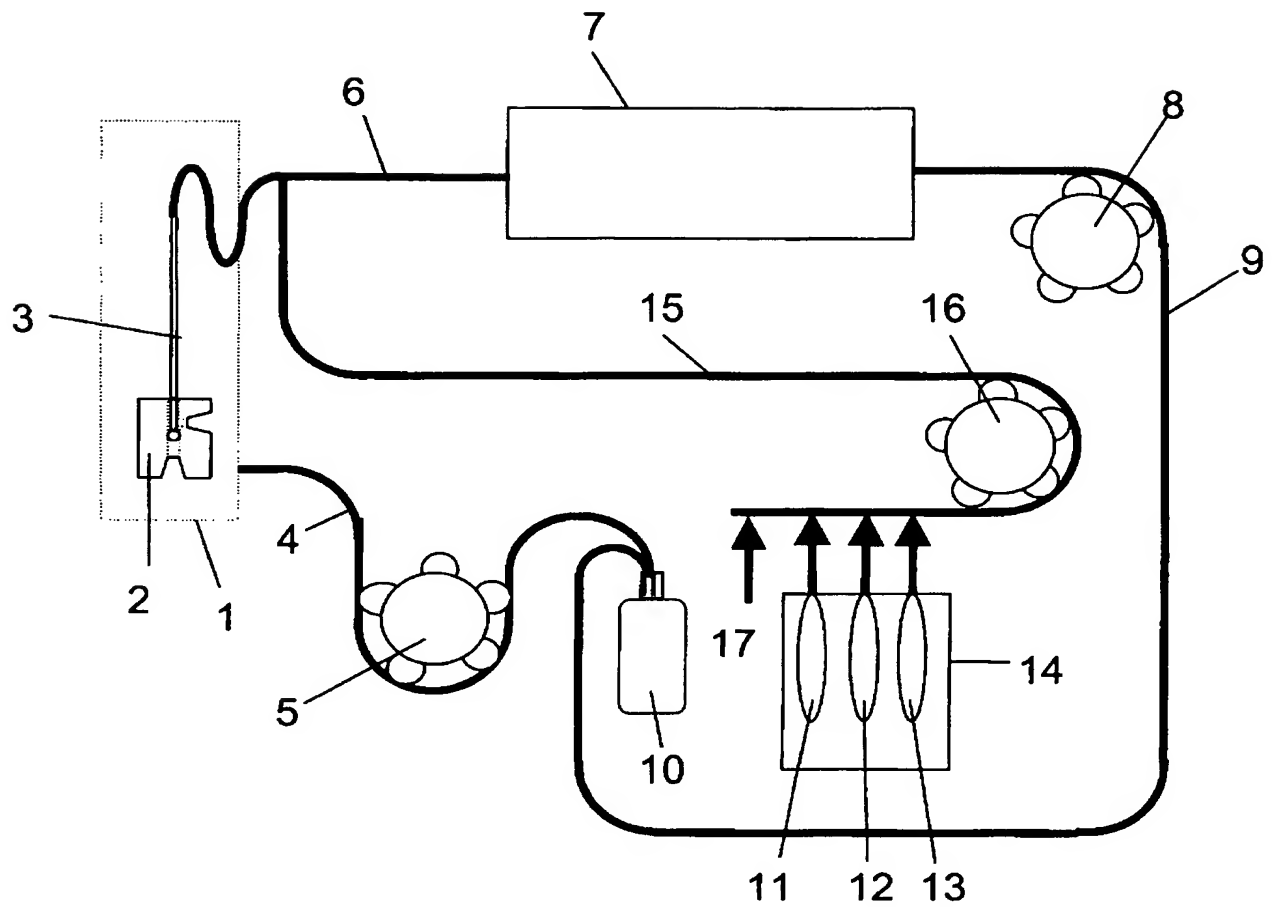


Fig. 1



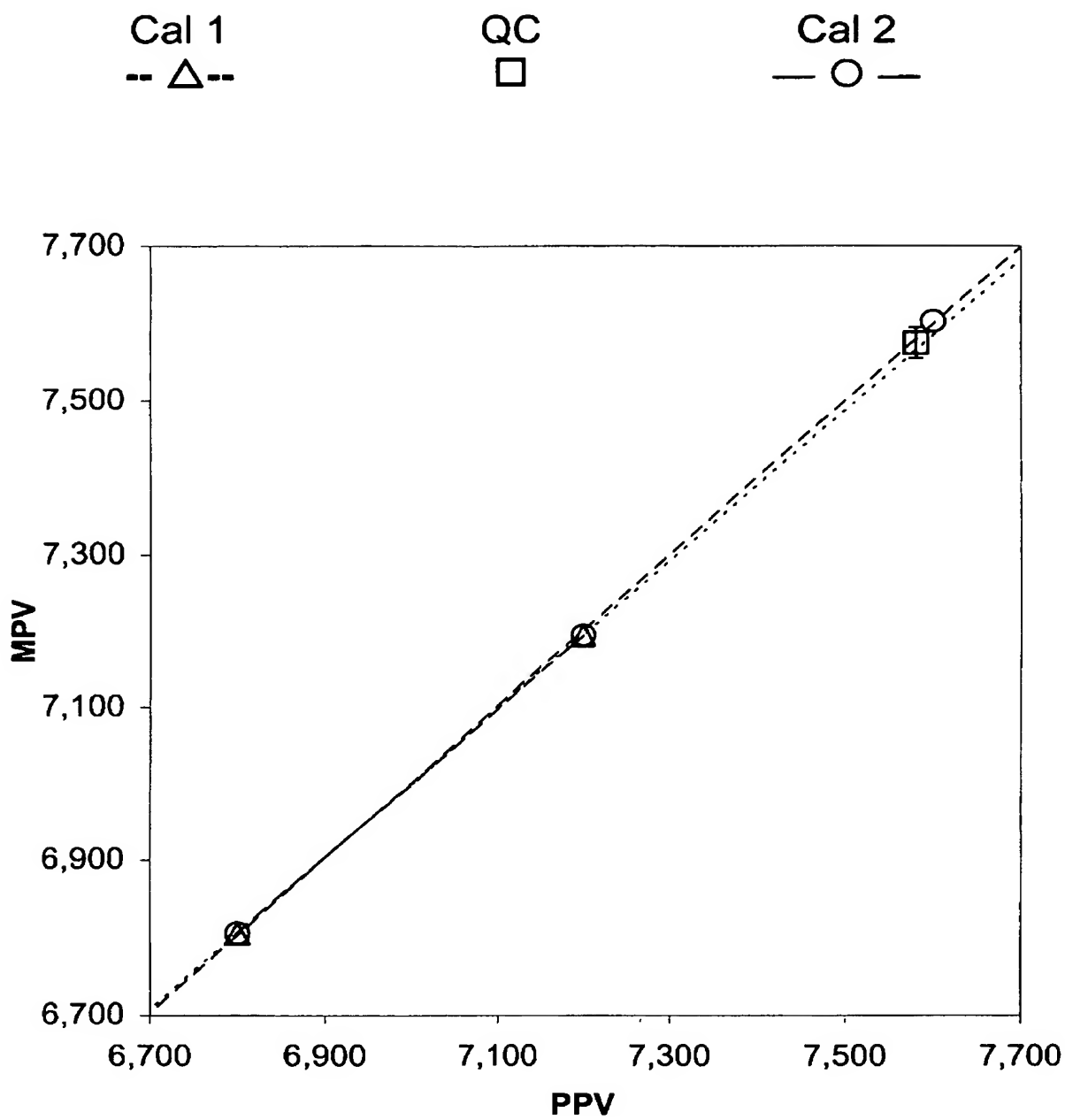


Fig. 2